

Amendments to the Claims:

USSN 10/520, 768

This listing of claims will replace all prior versions, and listings, of claims in the application.

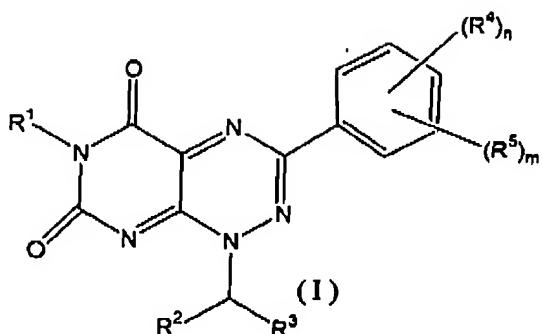
Claims 1-9, (canceled)

Claim 10. (canceled)

Claim 11. (canceled)

Claims 12-23, (canceled)

24. (New) A compound having the formula



and its N-oxide forms, pharmaceutically acceptable addition salts and stereo-chemically isomeric forms, wherein

n represents an integer being 0, 1 or 2.

m represents an integer being 0 or 1.

R^1 represents hydrogen, Ar^1 , C_{1-4} alkyl or C_{1-4} alkyl substituted with morpholino- 1 -methyl-

R^2 and R^3 taken together with the carbon atom to which R^1 is attached, form a 5-oxo-1,3-dihydro-2H-pyrazole-2,4-dimethyl or 3,4-dimethyl substituted with morpholinyl or

C_{3-8} cycloalkyl or Het¹ wherein said C_{3-8} cycloalkyl or Het¹ each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from C_{1-4} alkyloxycarbonyl, - C_{1-4} alkyl-Ar³

C₁₋₄alkylsulfonyl, aminosulfonyl, mono- or di(C₁₋₄alkyl)aminosulfonyl or -C(-NH₂)-NH-.

R^4 represents halo, nitro, hydroxy or C_1-C_6 alkyl oxy.

R^5 represents formyl, hydroxy, cyano, phenyl, CH_3^2 , ND_3^2 , or $CH_3^2ND_3^2$.

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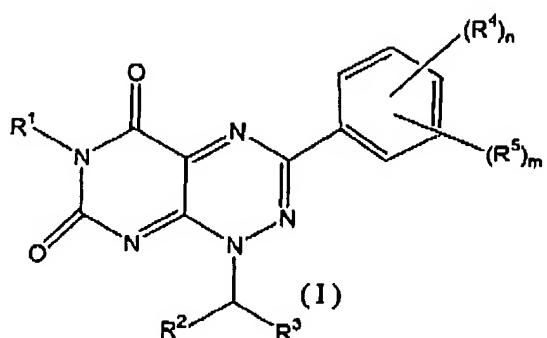
Claims 1-9. (canceled)

Claim 10. (canceled)

Claim 11. (canceled)

Claims 12-23. (canceled)

24. (New) A compound having the formula



and its N-oxide forms, pharmaceutically acceptable addition salts and stereo-chemically isomeric forms, wherein

n represents an integer being 0, 1 or 2;

m represents an integer being 0 or 1;

R¹ represents hydrogen, Ar¹, C₁₋₄alkyl or C₁₋₄alkyl substituted with morpholinyl or pyridinyl;

R² and R³ taken together with the carbon atom to which they are attached form a

C₃₋₈cycloalkyl or Het¹ wherein said C₃₋₈cycloalkyl or Het¹ each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from C₁₋₄alkyloxycarbonyl, -C₁₋₄alkyl-Ar³

C₁₋₄alkylsulfonyl, aminosulfonyl, mono- or di(C₁₋₄alkyl)aminosulfonyl or -C(=NH)-NH₂;

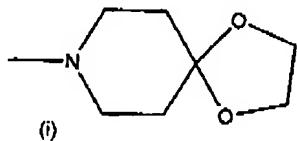
R⁴ represents halo, nitro, hydroxy or C₁₋₄alkyloxy;

R⁵ represents formyl, hydroxy, cyano, phenyl, -O-Ar², NR⁶R⁷, C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkylsulfonyl, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, -O-(mono- or di(C₁₋₄alkyl)aminosulfonyl), Het², -SO₂-Het³, C₂₋₆alkenyl optionally substituted with phenyl,

C₁₋₄alkyl substituted with one or where possible more substituent being selected from hydroxy, halo, Het³, NR⁶R⁷ or formyl,

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C_{1-4} alkyloxy substituted with one or where possible more substituents being selected from halo, amino, mono- or di(C_{1-4} alkyl)aminosulfonyl, aminosulfonyl, Het^4 , NR^8R^9 or $-C(=O)-Het^4$; R^6 and R^7 are each independently selected from hydrogen, C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl, Het^5 or C_{1-4} alkyl substituted with one or where possible more substituents being selected from hydroxy, Het^5 , C_{1-4} alkyloxycarbonyl, or C_{1-4} alkylsulfonyl; R^8 and R^9 are each independently selected from hydrogen, C_{1-4} alkyl, C_{1-4} alkyloxycarbonyl, Het^7 , mono- or di(C_{1-4} alkyl)aminosulphonyl or aminosulphonyl; Het^1 represents piperidinyl or dihydroindenyl; Het^2 represents a heterocycle selected from piperidinyl, morpholinyl, or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from C_{1-4} alkyloxycarbonyl; Het^3 represents a heterocycle selected from morpholinyl, pyrrolidinyl, pyrrolyl, piperidinyl, or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from hydroxy, C_{1-4} alkyl, C_{1-4} alkyloxycarbonyl, hydroxy C_{1-4} alkyl, aminosulfonyl, $NR^{10}R^{11}$, imidazolyl, tetrahydropyrimidinyl, amino, mono- or di(C_{1-4} alkyl)aminosulfonyl, hydroxy C_{1-4} alkyloxy C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl or C_{1-4} alkyloxy; R^{10} and R^{11} are each independently selected from hydrogen, C_{1-4} alkyl, C_{1-4} alkyloxycarbonyl, aminosulfonyl, or mono- or di(C_{1-4} alkyl)aminosulfonyl; Het^4 represents a heterocycle selected from morpholinyl, piperidinyl, imidazolyl or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from hydroxy, C_{1-4} alkyl, C_{1-4} alkyloxycarbonyl, aminosulfonyl or mono- or di(C_{1-4} alkyl)aminosulfonyl or Het^4 represents a monovalent radical represented by formula (i);



Het^5 represents a heterocycle selected from pyridinyl, pyrimidinyl, pyrrolidinyl, or piperidinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from C_{1-4} alkyl, C_{1-4} alkyloxycarbonyl, aminosulfonyl, C_{1-4} alkylaminosulfonyl or mono- or di(C_{1-4} alkyl)aminosulfonyl; Het^6 represents morpholinyl;

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Het⁷ represents pyridinyl, piperidinyl, piperazinyl or pyrimidinyl optionally substituted with C₁₋₄alkylphenyl, C₁₋₄alkyloxycarbonyl aminosulfonyl, or mono- or di(C₁₋₄alkyl)aminosulfonyl;

Ar¹ represents an aryl substituent selected from phenyl or naphthalenyl wherein said aryl substituents each independently may optionally be substituted with one, or where possibly two or three substituents each independently selected from nitro or C₁₋₄alkyloxycarbonyl;

Ar² represents phenyl optionally substituted with one or where possible two or three substituents each independently selected from the group consisting of halo and nitro;

Ar³ represents an aryl substituent selected from the group consisting of phenyl,

25. (New) A compound according to claim 24 wherein;

R¹ represents Ar¹, C₁₋₄alkyl, or C₁₋₄alkyl substituted with morpholinyl;

R² and R³ taken together with the carbon atom to which they are attached form a C₃₋₈cycloalkyl or Het¹ wherein said C₃₋₈cycloalkyl or Het¹ each independently may optionally be substituted with C₁₋₄alkyloxycarbonyl;

R⁴ represents halo or R⁴ represents C₁₋₄alkyloxy;

R⁵ represents C₁₋₄alkyloxycarbonyl, -O-(mono- or di(C₁₋₄alkyl)aminosulfonyl), C₁₋₄alkyl substituted with one or where possible more substituent being selected from Het³ or NR⁶R⁷,

C₁₋₄alkyloxy substituted with one or where possible more substituents being selected from amino, Het⁴ or NR⁸R⁹;

R⁶ and R⁷ are each independently selected from hydrogen, C₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl, Het⁵ or C₁₋₄alkyl substituted with one or where possible more substituents being selected from hydroxy or Het⁵;

R⁸ and R⁹ are each independently selected from hydrogen, C₁₋₄alkyl, C₁₋₄alkyloxycarbonyl, Het⁷ or mono- or di(C₁₋₄alkyl)aminosulfonyl;

Het¹ represents piperidinyl;

Het³ represents a heterocycle selected from morpholinyl, pyrrolidinyl, piperidinyl, or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from hydroxy, C₁₋₄alkyl, aminosulfonyl, amino, mono- or di(C₁₋₄alkyl)aminosulfonyl, hydroxyC₁₋₄alkyloxyC₁₋₄alkyl or C₁₋₄alkyloxy;

Het⁵ represents pyridinyl optionally substituted with mono- or di(C₁₋₄alkyl)aminosulfonyl;

Het⁷ represents piperidinyl optionally substituted with C₁₋₄alkylphenyl, C₁₋₄alkyloxycarbonyl, or mono- or di(C₁₋₄alkyl)aminosulfonyl;

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Ar¹ represents an aryl substituent selected from phenyl or naphthalenyl;

26. (New) A compound according to claim 24 wherein;

R¹ represents C₁₋₄alkyl;

R² and R³ taken together with the carbon atom to which they are attached form a C₃₋₆cycloalkyl or piperidinyl wherein said C₃₋₆cycloalkyl or Het¹ each independently may optionally be substituted with C₁₋₄alkyloxycarbonyl;

R⁴ represents halo or C₁₋₄alkyloxy;

R⁵ represents C₁₋₄alkyloxycarbonyl, -O-(mono- or di(C₁₋₄alkyl)aminosulfonyl),

C₁₋₄alkyl substituted with one or where possible more substituent being selected from Het³ or NR⁶R⁷,

C₁₋₄alkyloxy substituted with one or where possible more substituents being selected from amino, Het⁴ or NR⁸R⁹;

R⁶ and R⁷ are each independently selected from hydrogen, C₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl, - Het⁵ or C₁₋₄alkyl substituted with one or where possible more substituents being selected from hydroxy, or Het⁵;

R⁸ and R⁹ are each independently selected from hydrogen, C₁₋₄alkyl, -Het⁷ or mono- or di(C₁₋₄alkyl)aminosulphonyl;

Het³ represents a heterocycle selected from piperidinyl, or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from hydroxy, aminosulfonyl, amino, mono- or di(C₁₋₄alkyl)aminosulfonyl, hydroxyC₁₋₄alkyloxyC₁₋₄alkyl or C₁₋₄alkyloxy;

Het⁴ represents a heterocycle selected from morpholinyl, piperidinyl or piperazinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from C₁₋₄alkyl, C₁₋₄alkyloxycarbonyl or mono- or di(C₁₋₄alkyl)aminosulfonyl;

Het⁵ represents a heterocycle selected from pyridinyl or piperidinyl wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible two or three substituents each independently selected from aminosulfonyl, or mono- or di(C₁₋₄alkyl)aminosulfonyl;

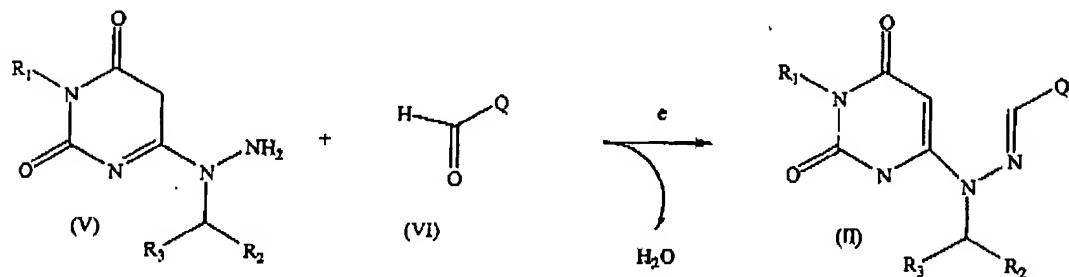
Het⁷ represents piperidinyl.

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27. (New) A compound as claimed in claim 24, wherein R² and R³ taken together with the carbon atom to which they are attached form a C₃₋₈cycloalkyl.
28. (New) A compound as claimed in claim 27, wherein R² and R³ taken together with the carbon atom to which they are attached are cyclopentyl.
- 29 (New) A compound according to claim 24 wherein R⁵ represents formyl, hydroxy, cyano, phenyl, -O-Ar², NR⁶R⁷, C₁₋₄alkylsulfonyl, C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonyl, -O-(mono- or di(C₁₋₄alkyl)aminosulfonyl), Het², -SO₂-Het⁶, C₂₋₈alkenyl optionally substituted with phenyl, C₁₋₄alkyl substituted with one or where possible more substituent being selected from hydroxy, halo, Het³, NR⁶R⁷ or formyl, or C₁₋₄alkyloxy substituted with one or where possible more substituents being selected from halo, amino, mono- or di(C₁₋₄alkyl)aminosulfonyl, aminosulfonyl, Het⁴, NR⁸R⁹ or -C(=O)-Het⁴.
30. (New) A compound according to claim 24, provided that when R⁵ represents NR⁶R⁷, either R⁶ or R⁷ represents C₁₋₄alkylsulfonyl or C₁₋₄alkylcarbonyl.
31. (New) A compound according to claim 30, provided that when R⁵ represents NR⁶R⁷, either R⁶ or R⁷ represents methylsulfonyl or methylcarbonyl.
32. (New) A compound as claimed in claim 24, provided that when R⁵ represents a C₁₋₄alkyloxy substituted Het⁴, said Het⁴ being selected from the group consisting of morpholinyl, piperidinyl, piperazinyl and piperazinyl substituted with one C₁₋₄alkyl substituent, or Het⁴ consists of piperazinyl substituted with one mono- or di(C₁₋₄alkyl)aminosulfonyl substituent.
33. (New) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, an effective kinase inhibitory amount of a compound as described in claim 24.

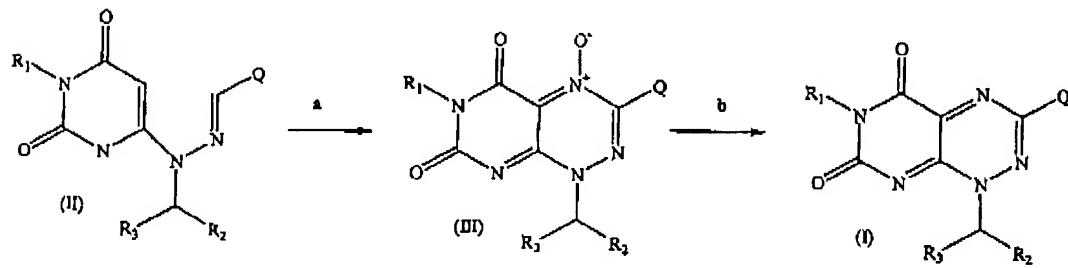
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34. (New) A process of preparing a compound as described in claim 24, comprising
 i) reacting a primary amine of formula (V) with an aldehyde of formula (VI) in a condensation reaction using ethanol as a suitable solvent;



e) EtOH

ii) followed by a nitrosative cyclisation of the thus obtained Schiffs bases of formula (II) with NaNO₂ in acetic acid, and refluxing the nitroso intermediates of formula (III) in a suitable solvent such as acetic anhydride or ethanol further comprising dithiothreitol (DTT);

a) NaNO₂, AcOH, H₂O b) DTT, EtOH

35. (New) A compound as claimed claim 24, wherein R² and R³ taken together with the carbon atom to which they are attached form a C₃₋₈cycloalkyl.

36. (New) A compound as claimed claim 35, wherein R² and R³ taken together with the carbon atom to which they are attached form cyclopentyl.

37. (New) A compound according to claim 24, provided that when R⁵ represents NR⁶R⁷, either R⁶ or R⁷ represents C₁₋₄alkylsulfonyl or C₁₋₄alkylcarbonyl.

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38. (New) A compound according to claim 37, provided that when R^5 represents NR^6R^7 , either R^6 or R^7 represents methylsulfonyl or methylcarbonyl.

39. (New) A compound according to claim 38, provided that when R^5 represents NR^6R^7 , either R^6 or R^7 represents methylsulfonyl.

40. (New) A compound according to claim 38, provided that when R^5 represents NR^6R^7 , either R^6 or R^7 represents methylcarbonyl.

41. (New) A compound as claimed in claim 24, provided that when R^5 represents a C_{1-4} alkyloxy substituted Het⁴, said Het⁴ being selected from the group consisting of morpholinyl, piperidinyl, piperazinyl and piperazinyl substituted with one C_{1-4} alkyl substituent, or Het⁴ consists of piperazinyl substituted with one mono- or di(C_{1-4} alkyl)aminosulfonyl substituent.

42. (New) A compound as claimed in claim 41, provided that when R^5 represents a C_{1-4} alkyloxy substituted Het⁴, said Het⁴ being selected from the group consisting of morpholinyl, piperidinyl, piperazinyl and piperazinyl substituted with methyl in the para position relative to the carbon atom bearing the R^5 substituent, or Het⁴ consists of piperazinyl substituted with dimethylaminosulfonyl in the para position relative to the carbon atom bearing the R^5 substituent.

43. (New) A compound as claimed in claim 25, provided that when R^5 represents a C_{1-4} alkyloxy substituted Het⁴, said Het⁴ being selected from the group consisting of morpholinyl, piperidinyl, piperazinyl and piperazinyl substituted with methyl in the para position relative to the carbon atom bearing the R^5 substituent, or Het⁴ consists of piperazinyl substituted with dimethylaminosulfonyl in the para position relative to the carbon atom bearing the R^5 substituent.

44. (New) A compound as claimed in claim 26, provided that when R^5 represents a C_{1-4} alkyloxy substituted Het⁴, said Het⁴ being selected from the group consisting of morpholinyl, piperidinyl, piperazinyl and piperazinyl substituted with methyl in the para position relative to the carbon atom bearing the R^5 substituent, or Het⁴ consists of piperazinyl substituted with dimethylaminosulfonyl in the para position relative to the carbon atom bearing the R^5 substituent.

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45. (New) A compound as claimed in claim 28, provided that when R^6 represents a C_{1-4} alkyloxy substituted Het⁴, said Het⁴ being selected from the group consisting of morpholinyl, piperidinyl, piperazinyl and piperazinyl substituted with methyl in the para position relative to the carbon atom bearing the R^5 substituent, or Het⁴ consists of piperazinyl substituted with dimethylaminosulfonyl, in the para position relative to the carbon atom bearing the R^5 substituent.